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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/717,450	11/20/2000	Lisa Ann Neuhold	0630/D532US1	5417

32801 7590 11/07/2005

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/717,450	NEUHOLD ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-57,59-68,72-77 and 79-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-57,59-64,66-68,72-77,79 and 81-100* is/are rejected.

7)☒ Claim(s) *65 and 80* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION
Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-2-05 has been entered.

Applicant's arguments and the Declaration by Roger Askew filed 9-2-05 have been fully considered and is discussed below.

Claims 58, 69-71 and 78 have been cancelled. Claims 98-100 have been added. Claims 55-57, 59-68, 72-77 and 79-100 are pending and under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Written description

1. Claims 55-57, 59-64, 66-68, 72-77, 79 and 81-97 remain rejected and claims 98-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 65 and 80 have been withdrawn from the rejection because the claims are limited to a transgenic rat made using a type II collagen promoter.

The written description rejection regarding the phrase "joint-specific promoter" has been withdrawn because the phrase has been replaced with "chondrocyte-specific promoter." However, the new phrase is also rejected for reasons of record.

The phrase "chondrocyte-specific promoter" as newly amended lacks written description because the specification does not disclose any promoters that meet the description of "chondrocyte-specific promoters" provided in the specification other than the type II collagen promoter.

Pg 16, lines 7-13, describes the function of the promoter as being "joint-specific" (the transcriptional activator polypeptide under the control of a joint-specific promoter...."

Pg 15, line 19, though pg 16, line 9, defines the function of "joint-specific promoters" ("Promoters that direct transcription selectively in joint tissues. Joint-specific expression as used herein refers to expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% of the level

of expression in joints. Preferably, expression in non-joint tissues is undetectable. Useful promoter sequences that confer joint-specific expression on a sequence to which they are operably linked to include without limitation sequences derived from the collagen type II promoter"). The specification only describes the structure of one promoter having the function defined in the specification. Describing the structure of one species within a genus defined by function is not adequate written description of other structures within the genus. Other promoters that meet the definition on pg 15, lines 19, through pg 16, line 9 may not exist.

Pg 6, lines 15-20, refers to "joint-specific promoters", specifically type II collagen promoter, but does not describe the structure of any other promoters having the same function.

Pg 36, lines 21, through pg 37, line 1, refers to a "joint-specific promoter (type II collagen", but does not describe the structure of any other promoters having the same function.

Pg 40, lines 1-22, Example 4 describes obtaining "joint specific expression conferred by type II collagen promoter" but does not describe any promoter other than type II collagen promoter having such function.

Given the teachings in the specification, the limitation of "chondrocyte-specific promoter" is limited to the definition of "joint-specific expression" on pg 15, line 19-20, i.e. expression that is greater in chondrocytes than in other tissues; typically, the level of expression in non-joint tissues is less than 10%.

Defining the function of what applicants consider "joint-specific promoters" without describing the structure of adequate numbers of promoters having that function is simply a wish to identify promoters having that function. Defining the function of a promoter without describing the structure of a representative number of promoters

having that function or comparing the structure of type II collagen promoter to other promoters, is not adequate description of "joint-specific promoters." Accordingly, describing a rat having a type II collagen promoter fails to describe the genus of rats having a "chondrocyte-specific promoter" as claimed. Adequate written description of a rat having a "chondrocyte-specific promoter" requires more than a mere statement that it is part of the invention. What is required is a description of a reasonable number of rats having such promoters. Defining what applicants consider the function of a "chondrocyte-specific promoter" without describing the structure of promoters having that function is simply a wish to identify promoters having that function that can be used to make the rat claimed. Naming a promoter that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Applicants argue the broader concept of the rats in the claims overcomes the lack of written description of the narrower concept of "chondrocyte-specific promoters" used to make the rat. Applicants' argument is not persuasive. Without adequately describing the elements used to make the rat, the specification cannot adequately describe the rat. The rat claimed does not have adequate written description because "chondrocyte-specific promoters" used to make the rat (other than type II collagen promoter) do not have adequate written description.

Applicants argue the specification described promoters that direct transcription in joint tissues on pg 15, line 19, through pg 16, line 6, and provides an example of expressing an enzyme in chondrocytes (the cells found in cartilage). Applicants conclude that the principle of "chondrocyte-specific promoters" was established with an

example and that those of skill would recognize that "joint (i.e., chondrocyte)-specific expression of MDE, particularly a collagen II-degrading MMP, would yield the desired joint degradation." Applicants' argument is not persuasive. The specification does not teach the structure of any "chondrocyte-specific promoters" other than the type II collagen promoters. Accordingly, the specification fails to provide adequate written description for a rat having any "chondrocyte-specific promoter" as broadly claimed.

Applicants argue "chondrocyte-specific promoters" were known in the art at the time of filing. Applicants provide a declaration by Roger Askew who refers to Pirok (J. Biol. Chem., 1997, Vol. 272, pg 11566-11574) who taught the chick aggrecan promoter and Lefebvre (EMBO, May 1998, Vol. 17, No. 19, pg 5718-5733) who taught the Sox6 and Sox9 transcription factors which provide chondrocyte-specific expression of the col2a1 gene as well as two promoters, the col2a1 and col11a2 promoters that lead to chondrocyte-specific expression (pg 5719, col. 1, 1st and 2nd full ¶). Applicants argue Lefebvre was published in May 1998 but represents work done in 1997. Applicants' arguments are not persuasive. The phrase "chondrocyte-specific promoter" in context of the specification is limited to a promoter that provides expression that is greater in chondrocytes than in other tissues; typically, the level of expression in non-chondrocytes is less than 10% (pg 15, lines 19-20). Pirok and Lefebvre fail to indicate the chick aggrecan promoter, the col2a1 or col11a2 promoters provide such expression. The last line in the abstract of Pirok merely states the aggrecan regulatory region is important "in the tissue specific expression of the chick aggrecan gene." Pirok merely compared expression of the chick aggrecan promoter in chicken chondrocytes and fibroblasts in vitro; Pirok did not teach the aggrecan promoter provided expression in chondrocytes while providing less than 10% expression in non-chondrocytes. Furthermore, Pirok taught the chick aggrecan promoter does not correlate to the mouse

or rat promoter (pg 11567, 1st full ¶); therefore, one of skill would not necessarily expect the chick promoter to have the same specificity in a rat. Lefebvre merely taught the col2a1 and col11a2 promoters comprised enhancers that provided expression in chondrocytes. Lefebvre did not teach promoters that were chondrocyte-specific or that the col2a1 or col11a2 enhancers provided expression in chondrocytes while providing less than 10% expression in non-chondrocytes as required in the instant application. In conclusion, paragraph 8 of the declaration is not persuasive because Pirok and Lefebvre did not teach promoters that meet the definition of a "joint-specific promoter" defined in the specification, because the col2a1 and col11a2 enhancers described by Lefebvre are not promoters and because the declaration does not provide any reasoning why the chick aggrecan promoter or the col2a1 and col11a2 enhancers meets the definition of a "joint-specific promoter" provided in the specification or why the chick promoter would have such function in a rat.

Applicants argue "chondrocyte-specific promoters" were well known in the art (pg 23, 1st full ¶, of arguments). Applicants argue the Second Neuhold Declaration (Exhibit 5 filed April 30, 2002 in the instant application) supports that other "chondrocyte-specific promoters" were known in the art. The Second Neuhold Declaration states the CD-RAP/MIA promoter may be substituted for the type II collagen promoter (¶ 7). Applicants' arguments are not persuasive. The Second Neuhold Declaration does not teach any other promoters known in the art that meet applicants' definition of "chondrocyte-specific promoters". The Second Neuhold Declaration, ¶ 7, merely states the identity of other promoters within the genus "is not important." While the declaration states the CD-RAP/MIA promoter may be substituted for the type II collagen promoter (¶ 7), the declaration does not discuss how the CD-RAP/MIA promoter meets the

functional definition of a "joint-specific promoter" provided in the specification (the level of expression in non-joint tissues is less than 10%).

Applicants argue, "[a]s set forth in the Second Neuhold Declaration (paragraph 7) the specific promoter employed to achieve tissue specific expression does not make any difference" (pg 23, 1st full ¶). Applicants' argument is not persuasive. Reference to a genus of promoters, while wishing to know other promoters within the genus, is at the heart of the law. The wish to know promoters within a genus defined by function without providing a representative number of examples by structure or structural features common to the members of the genus fails to meet the description requirements. Accordingly, the genus of rats having a "chondrocyte-specific promoter" as claimed taken with the definition of such promoters on pg 15, lines 19-20, fails to meet the written description requirements because the structure of rats having any promoter other than the type II collagen promoter has not been adequately described.

Applicants argue other "specific promoters" have been issued in US Patents 5,625,124, 5,880,327, 5,917,123 and 6,028,245. Applicants' arguments regarding 5,625,124 5,880,327; 5,917,123; 6,028,245 are moot because each patent is examined on its own merits and because none of the patents have promoters that meet applicants' definition of "joint-specific promoters."

Enablement

The enablement rejection regarding a transgenic rat expressing human MMP that cleaves type II collagen to a level sufficient to cause type II collagen degradation as claimed has been withdrawn in view of applicants' arguments in part. The specification teaches transgenic rats (claim 8 as originally filed). Methods of making transgenic rats were known in the art at the time of filing (Mullins (1990) and Hammer (1990) both of

record). As asserted by applicants in the arguments filed 9-2-05, MMPs and type II collagen are highly conserved across humans, rats and mice. No evidence can be found to the contrary. The specification teaches making transgenic mice expressing human MMP13 that degrades type II collagen to a level that causes type II collagen degradation. Without evidence to the contrary, human MMPs that degrade type II collagen in transgenic mice would also be expected to degrade type II collagen in transgenic rats. In addition, Howland (PNAS, Feb. 5, 2002, Vol. 99, No. 3, pg 1604-1609) taught making a transgenic rat that expresses the human $SOD1^{G93A}$ mutation found in patients with ALS (using a method of making transgenic rats known in 1983 (pg 1604, col. 2 last full ¶, reference 26)). The clinical and pathological changes of the rat resemble the 'high expressing' phenotype of $SOD1^{G93A}$ transgenic mice described earlier by Gurney in 1994 (pg 1609, col. 1, lines 1-7). Accordingly, the specification taken with the art at the time of filing provides adequate guidance for one of skill to overcome the unpredictability described by Mullins (1990, Nature, Vol. 344, pg 541-544), Hammer (1990, Cell, Vol. 63, pg 1099-1112), Mullins (1989, EMBO, Vol. 8, pg 4065-4072); and Taurog (1988, J. Immunol., Vol. 141, pg 4020-4023), all of record, and reasonably obtain a transgenic rat expressing a human MMP that cleaves type II collagen to a level sufficient to cause type II collagen degradation as claimed.

Wall of record (1996, Theriogenology, Vol. 45, pg 57-68) has been withdrawn because it relates to predicting the phenotype of transgenic livestock based on transgenic mice and does not compare the phenotype of transgenic rats and mice.

Ebert of record (1988, Mol. Endocrinology, Vol. 2, pg 277-283) has been withdrawn because it relates to predicting the phenotype of a transgenic pig expressing a growth factor based on transgenic mice expressing a growth factor and does not compare the phenotype of transgenic rats and mice.

2. Claims 54-57, 59-64, 66-68, 72-77, 79 and 81-97 remain rejected and claims 98-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic rat or mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the rat or mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat or mouse during adulthood to a level sufficient to cause degradation of type II collagen, does not reasonably provide enablement for any "chondrocyte-specific promoter". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

THE CLAIMS

Claims 55-57, 59-64, 66-68, 72-77, 79 and 81-97 encompass transgenic rats made using a "chondrocyte-specific promoter" and methods related thereto. Claims 98-100 encompass methods of using a transgenic mouse having a "chondrocyte-specific promoter".

Claims 65 and 80 are excluded from the rejection because they are limited to transgenic rats made using the type II collagen promoter.

TEACHINGS IN THE SPECIFICATION AND CLAIM INTERPRETATION OF "CHONDROCYTE-SPECIFIC PROMOTER"

Pg 16, lines 7-13, describes the function of the promoter as being "joint-specific" (the transcriptional activator polypeptide under the control of a joint-specific promoter...."

Pg 15, line 19, though pg 16, line 9, defines the function of "joint-specific promoters" ("Promoters that direct transcription selectively in joint tissues. Joint-specific expression as used herein refers to expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% of the level of expression in joints. Preferably, expression in non-joint tissues is undetectable. Useful promoter sequences that confer joint-specific expression on a sequence to which they are operably linked to include without limitation sequences derived from the collagen type II promoter"). The specification only describes the structure of one promoter having the function defined in the specification. Describing the structure of one species within a genus defined by function is not adequate written description of other structures within the genus. Other promoters that meet the definition on pg 15, lines 19, through pg 16, line 9 may not exist.

Pg 6, lines 15-20, refers to "joint-specific promoters", specifically type II collagen promoter, but does not describe the structure of any other promoters having the same function.

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Pg 40, lines 1-22, Example 4 describes obtaining "joint specific expression conferred by type II collagen promoter" but does not describe any promoter other than type II collagen promoter having such function.

Given the teachings in the specification, the limitation of "chondrocyte-specific promoter" is limited to the definition of "joint-specific expression" on pg 15, line 19-20, i.e. expression that is greater in chondrocytes than in other tissues; typically, the level of expression in non-joint tissues is less than 10%.

WORKING EXAMPLES

The specification explicitly teaches making a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mouse. Expression is controlled by the administration/withdrawal of tetracycline or other regulatory compound. The working examples are limited to the type II collagen promoter.

AMOUNT OF EXPERIMENTATION

While one of skill could determine whether a promoter provided less than 10% expression in non-chondrocytes in a transgenic mouse or rat, no amount of experimentation would ensure that such a promoter existed. If no promoter provides less than 10% expression in non-chondrocytes as described in the specification, any assay to determine whether a promoter provides such expression would be undue.

REJECTION OF "CHONDROCYTE-SPECIFIC PROMOTERS" - PROMOTERS THAT CAUSE LESS THAN 10% EXPRESSION IN NON-CHONDROCYTES

The specification and the art do not teach the Type II collagen promoter or any other promoter causes expression greater in chondrocytes than other tissues or causes less than 10% expression in non-chondrocytes. Assuming argueno that the Type II collagen promoter causes less than 10% expression in non-chondrocytes, one species does not enable the genus because no other such promoter may exist. As such, a transgenic mouse or rat having a type II collagen promoter does not enable the genus of a transgenic mouse or rat having a "chondrocyte-specific promoter." Merely defining a "chondrocyte-specific promoter" without teaching any promoters that meet the definition is not an enabling disclosure.

ARGUMENTS

Applicants argue any promoter that functions in chondrocytes can be used in the instant invention. Applicants' argument is not persuasive. The claims are limited to "chondrocyte-specific promoters," which are limited to those that cause less than 10% expression in non-chondrocytes according to pg 15, lines 19-24. The claims do not encompass any promoter that functions in chondrocytes. The specification does not describe the type II collagen promoter or any other promoter causes less than 10% expression in non-chondrocytes.

Claim Rejections - 35 USC § 112 – indefiniteness

The previous rejection of claims 90-97 under indefiniteness has been withdrawn in view of the amendment.

3. Claims 90-97 remain rejected and claims 98-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 90-96 as newly amended and new claims 98-100 are indefinite because the phrase "the phenotypic change" at the end of claims 90-96 and 98 lacks antecedent basis. Replacing the phrase with –degradation of Type II collagen in joints— as in the preamble of the claims would overcome this rejection.

Art

The claims remain free of the prior art of record.

Claim Objection

Claims 65 and 80 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER